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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,422	06/25/2002	Michael Cawthorne	0380-P02754USO	3305

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EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 04/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,422	CAWTHORNE ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,14-25,27-34 and 38-53* is/are pending in the application.

4a) Of the above claim(s) *34 and 38-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,14-25,27-33,52 and 53* is/are rejected.

7)☒ Claim(s) *29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Specification

The objection to the disclosure for containing an embedded hyperlink and/or other form of browser-executable code is withdrawn in view of amendments made to the instant specification, filed 01/23/2006.

Claim Objections

The objection of claim 2 for an informality is withdrawn in view of amendments made to the instant claim.

The objection of claim 53 as not conforming to 37 CFR §1.75(c) is withdrawn in view of amendments made to the instant claim,

Claim 29 is objected to as the instant claim reads on non-elected protein and combinations of proteins rather the elected protein of LOMT21. For the purpose of continuing examination, claim 29 has been examined only to the extent of the elected protein, LOMT21. This objection is maintained and reiterated from the previous Office action.

Claim Rejections - 35 USC § 112, First Paragraph

The rejection of claims 1-7, 14-25, 27-32, and 52 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a biological sample

comprising cellular tissue, does not reasonably provide enablement for a subcellular fraction is withdrawn in view of amendments made to the instant claims.

Claim Rejections - 35 USC § 112, second paragraph

The previous rejection of claim 15 as being indefinite is withdrawn in view of arguments presented by applicants.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-7, 14-25, 27-33, 52, and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "comparatively insulin-sensitive subject" in lines 22 and 27 of the instant claim. Similarly, claims 5, 16, and 53 each recite the limitation of "comparatively insulin-sensitive subject" in line 2 of claim 5, line 4 of claim 16, and line 2 of claim 53. It is unclear from the instant claims what sample or subject to which a comparison is being made in order to arrive at a determination of a "comparatively insulin-sensitive subject." Claims 2, 3, 6, 7, 14, 15, 17-25, 27-33, and 52 are also included under this rejection due to their dependence from claim 1.

For the purpose of continuing examination, it is construed that a comparatively insulin-sensitive subject is a subject wherein its insulin sensitivity is more sensitive than an insulin-resistant subject as recited in step (a)(i) (lines 19 and 20 of instant claim 1).

Claim Rejections - 35 USC § 102

The previous rejection of claims 16 and 17 under 35 USC § 102(b) as being anticipated by Wang et al. is withdrawn in view of amendments made to the instant claims.

The previous rejection of claims 1, 6, 7, 18, 22, 23, and 52 under 35 USC § 102(b) as being anticipated by Stephens et al. is withdrawn in view of amendments made to the instant claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 3, 5, 14, 15, 18-20, 27, 28, 52, and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al.

The instant claims are drawn to a method of screening for an agent having efficacy in treating insulin resistance comprising providing a first biological sample obtained from an insulin resistant subject, a second biological sample obtained from a normal or comparatively insulin-sensitive subject, a third biological sample obtained from an insulin resistant subject who has been treated with a known treatment or compound which alters insulin sensitivity, and a fourth biological sample obtained from a normal or comparatively insulin-sensitive subject who has been treated with a known treatment or compound which alters insulin sensitivity. The method further comprises

identifying at least one differentially expressed protein which is differentially expressed in said first and second biological samples, differentially expressed in said first and third biological samples, but not differentially expressed in said second or fourth biological samples. The method further comprises providing a fifth biological sample comprising cellular tissue or a subcellular fraction thereof from an insulin resistant subject ,wherein said sample or subject has been treated with an agent, and determining the expression level of said at least one differentially expressed protein in said fifth sample, wherein agents which alter the expression of the level towards that observed in the second or third biological sample have efficacy for the treatment of insulin.

[Claims 1, 2, 3, 5, 14, 18-20, and 53]: Wang et al. sets forth that thiazolidinediones enhance insulin action and lower blood glucose in obese, insulin-resistant animals and patients with gluocose intolerance or non-insulin-dependent diabetes (see Wang et al., page 1045, col. 1, lines 1-10). Wang et al. further identifies that that troglitazone and the potent novel thiazolidinedione BRL 49653 (rosiglitazone) improves glucose tolerance, lowers hyperinulinaemia and up-regulates insulin receptors in peripheral tissues (see Wang et al., page 1045, col. 1, line 11 through page 1406, col. 1, line 13). To this end, Wang et al. sets forth a study that characterizes the effects of BRL 49653 on insulin resistance in Zucker and Wistar rats, which reads on the claimed method for screening for an agent having efficacy in treating insulin resistance. Expression levels of insulin were determined from several biological samples taken from both control (a normal subject, sample 2) and BRL 49653 treated (a normal subject treated with a compound that alters insulin sensitivity, sample 4) lean Zucker rats as

well as control (an insulin resistant subject, sample 1) and BRL 49653 treated (an insulin resistant subject treated with a compound that alters insulin sensitivity, sample 3) fatty Zucker rats, which reads on the claimed steps of providing a first through fourth biological sample (see Wang et al., Tables 1 and 2 and page 1406, col. 1, lines 14 through col. 2, line 22). Wang et al. further characterizes the differential expression insulin in the above identified rats wherein control lean Zucker rats (sample 2) expressed at 32.0 +/- 8.4; 7-day BRL 49653 treated lean Zucker rats (sample 4) expressed at 28.2, +/- 4.3; control fatty Zucker rats (sample 1) expressed at 397.4, +/- 26.8; and 7-day BRL 49653 treated fatty Zucker rats (sample 3) expressed at 279.1, +/- 20.8 (see Wang et al., Tables 1 and 2). As such, insulin was identified as being differentially expressed between the first and second samples (397.4, +/- 26.8 vs. 32.0, +/- 8.4), differentially expressed between the first and third samples (397.4, +/- 26.8 vs. 297.1, +/- 20.8), but not differentially expressed between the second and forth samples (32.0, +/- 8.4 vs. 28.2, +/- 4.3), which reads on step of identifying at least one differentially expressed protein. In the instant case, the treatment of fatty Zucker rats with BRL 49653 reads on the claimed limitation of providing a fifth biological sample from a subject that has been treated with an agent, as the instant claims do not exclude the embodiment wherein the screened agent may also be the compound that alters insulin sensitivity. As such, the BRL 49653 compound acts as an agent which alters the expression level of insulin to that observed in the above identified third biological sample.

[Claim 15]: Wang et al. provides for the male lean Zucker rats to be either heterozygous or homozygous for the Fa gene (Fa/?), and that fatty Zucker rats are heterozygous for the recessive fa gene (fa/fa) (see Wang et al., page 1406, col. 1, lines 16-22). As such, through simple Mendalian genetics the normal subjects, i.e. lean Zucker rats (Fa/?), may inherently be litter mates of the insulin resistant fatty Zucker rats (fa/fa) (see also pages 21 and 22 of applicants response, filed 01/23/2006).

[Claims 27 and 28]: Wang et al. sets forth the isolation and measurement of insulin in the disclosed methodology as well as the characterization the role of insulin and BRL 49653 in the insulin action on both Wistar and Zucker rats (see Wang et al., page 1405, col. 1, lines 1-25 and page 1406, col. 1, line 50 through col. 2, line 22).

[Claim 33]: Wang et al. sets forth the preparation of daily BRL 49653 dosages in a 10% sucrose solution and orally administering to Zucker rats relied upon in the study (see Want et al., page 1406, col. 1, lines 29-48).

[Claim 52]: Wang et al. sets forth that the results of the study demonstrates a previous observation that thiazolidinediones, specifically by the administration of effective amount of BRL 49653, have an impact on insulin resistant subjects (see Wang et al., page 1407, col. 1, line 34 through col. 2, line 4).

Claim Rejections - 35 USC § 103

The rejection of claims 1-3, 5-7, 14, 16-20, 22, 23, 27-33, and 52 as being unpatentable over Stephens et al. in view of Linskens et al. is withdrawn in view of amendments made to the instant claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 3, 5, 14, 15, 18-20, 27, 28, 52, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. as applied to claims 1, 2, 3, 5, 14, 15, 18-20, 27, 28, 52, and 53 above, and further in view of Linskens et al. (U.S. Patent No. 5,744,300).

The instant claims are drawn to a method of screening for an agent having efficacy in treating insulin resistance comprising providing a first through fourth biological sample, identifying at least one differentially expressed protein using said biological samples, providing a fifth biological sample comprising cellular tissue or a subcellular fraction thereof from an insulin resistant subject ,wherein said sample or subject has been treated with an agent, and determining the expression level of said at least one differentially expressed protein in said fifth sample, wherein agents which alter the expression of the level towards that observed in the second or third biological sample have efficacy for the treatment of insulin. The instant claims are further drawn to

a method wherein agents or proteins are screened using a high throughput screening method.

[Claim 32]: As discussed above, Wang et al. sets forth a study of BRL 49653 in Zucker and Wistar rats, which reads on the claimed method for screening for an agent having efficacy in treating insulin resistance. However, Wang et al. does not fairly teach or suggest a method wherein agents or proteins are screened using a high throughput method.

Linskens et al. sets forth, in the context of senescence-related genes, methods of high-throughput screening to identify compounds which alter differential expression levels. See Linskens et al., Abstract and claim 1. Linskens et al. further provide for the isolation and characterization of the differentially expressed genes and related gene products. See Linskens et al., column 4, line 34 through column 5, line 11. Linskens et al. further sets forth the use of identified genetags correlated with known sequences for use in high-throughput assays to quantify differential gene expression in response to treatment with active compounds. See Linskens et al., column 13, line 44 through column 14, line 35. Identified genetags have been established for, amongst many others, human aldehyde dehydrogenase 1 and human insulin-like growth factor binding protein 5. See Linskens et al., column 13, lines 13-43.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ the high throughput methodology of identifying differentially expressed genes taught by Linskens et al. for isolating and characterizing the differentially expressed proteins

identified by Wang et al. because the isolating, characterizing, and high-throughput techniques taught by Linskens et al. are generally applicable to systems comprising differentially expressed genes.

Response to Arguments

Applicant's arguments filed 01/23/2006 have been fully considered but they are not persuasive.

Applicants arguments traversing the restriction requirement, mailed 01/26/2006, are acknowledged. However, the traversal of the restriction requirement has been addressed in the previous Office action mailed 09/16/2005 and made final. As such, the traversal arguments presented in the response filed 01/23/2006 are not germane to the instant prosecution.

In regards to Wang et al., applicants argue that the reference does not disclose the instantly claimed screening method. Specifically, applicants argue that Wang et al. discloses a number of proteins that vary in animal models when treated with the known insulin-sensitizing drug rosiglitazone, however it does not suggest the levels of these proteins can be used as markers in a screen to identify new agents for treating insulin resistance.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies

(i.e., using protein markers in a screen to identify new agents for treating insulin resistance) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is noted that Wang et al. sets forth a method of analysis in order to determine the efficacy of thiazolidediones on insulin resistant animals and further characterizes the roles of various proteins (including insulin) in insulin resistance activity (see Wang et al., page 1405, col. 1, line 1 through page 1406, col. 1., 13). To this end, the study disclosed by Wang et al. tested a previous hypothesis that over activity of the ARC NPY neurones mediates hyperphagia induced by rosiglitazone, which reads on a method for screening an agent (in the instant case, rosiglitazone) for having efficacy in treating insulin resistant subjects. Further, the instant claims are not limited to embodiments wherein the screened agents are new or previously uncharacterized compounds, but rather is open to embodiments wherein the agent may also be the compound that is used the claimed steps for identifying at least one differentially expressed protein (i. e. steps a) and b) of instant claim 1).

Applicants further argue that the basis of the rejection wherein rosiglitazone alters the expression of NPY, leptin, and insulin in insulin resistant Zucker rats is incorrect.

In response, it is noted that Wang et al. discloses rosiglitazone effects the expression of several different proteins. Further, the instant rejection is based upon the

differential expression patterns of insulin derived from several biological samples taken from lean and fatty Zucker rats treated with rosiglitazone. As such, the expression of NPY, leptin, and insulin is not relied upon in the basis of the instant rejection.

Applicants further argue that Wang et al. does not disclose a method having all the steps as currently recited in claim 1, in that the reference fails to teach the steps of identifying marker protein or proteins as recited in steps a) and b) of the instant claim.

In response, it is reiterated from the above rejection that Wang et al. sets forth expression levels of isulin determined from several biological samples taken from both control (a normal subject, sample 2) and BRL 49653 treated (a normal subject treated with a compound that alters insulin sensitivity, sample 4) lean Zucker rats as well as control (an insulin resistant subject, sample 1) and BRL 49653 treated (an insulin resistant subject treated with a compound that alters insulin sensitivity, sample 3) fatty Zucker rats, which reads on the claimed steps of providing a first through fourth biological sample. Wang et al. further characterizes the differential expression insulin in the above identified rats wherein control lean Zucker rats (sample 2) expressed at 32.0 +/- 8.4; 7-day BRL 49653 treated lean Zucker rats (sample 4) expressed at 28.2, +/- 4.3; control fatty Zucker rats (sample 1) expressed at 397.4, +/- 26.8; and 7-day BRL 49653 treated fatty Zucker rats (sample 3) expressed at 279.1, +/- 20.8 (see Wang et al., Tables 1 and 2). As such, insulin was identified as being differentially expressed between the first and second samples (397.4, +/- 26.8 vs. 32.0, +/- 8.4), differentially expressed between the first and third samples (397.4, +/- 26.8 vs. 297.1, +/- 20.8), but

not differentially expressed between the second and forth samples (32.0, +/- 8.4 vs. 28.2, +/- 4.3), which reads on step of identifying at least one differentially expressed protein.

In regards to the rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Wang et al. in view of Linskens et al., applicants argue that Linskens et al. does not analyze differentially protein expression but rather is directed to methods of identifying senescence-related genes by comparing mRNA levels in senescent cells and young quiescent cells.

In response, it is noted that the instant rejection relies upon Linskens et al. for the teaching of an application of a high throughput screening method applied to differentially expressed proteins. As set forth in the above rejection, Wang et al. is relied upon in the instant rejection as teaching the limitations recited in instant claim 1. The methodology disclosed of Linskens et al. provides for an advantageous high throughput application of "enhanced differential display" (EDD) involving the use of PCR amplification to provide a representative of differentially expressed mRNA populations within a given sample. The use of EDD is demonstrated to display the different mRNA population levels present in a given sample and allows for differentially expressed genes to be selectively identified and further characterized (see especially Linskens et al., col. 6, lines 24-57). As such, the high throughput methodology as taught by Linskens et al. is generally applicable to identifying any differentially expressed genes and not limited to the specific application of identifying senescence-related genes. Further, the differentially expressed proteins

disclosed by Wang et al. must be accompanied in by corresponding differentially expressed levels of mRNA in the disclosed tissue sample, which can be taken advantage of in applying an EDD high throughput method. It is further noted that instant claim 32 does not recite any limitation that specifies what the claimed high throughput method must include.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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EDJ EDJ

11 April 2006

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER